

REMARKS

Claims 3, 8, 39, 52 and 56 have been amended to more clearly describe Applicants' invention. Support for the amendments can be found, for example, at page 7 lines 16-19, at page 11, Table 1 and at page 18, Table 8. Claims 57-64 are new. Support for the new claims can be found, for example, at page 7 lines 16-19, at page 11, Table 1 and at page 19, Table 8. No new matter has been added. Applicants wish to respectfully draw the Examiner's attention to the fact that claims 3, 4, 6, 8-12, 14, 30-35, 37-52, 54 and 56 were pending before this amendment, rather than claims 3, 8, 9, 14, 30-35, 37-52, 54 and 56 as listed by the Examiner in the Office Action. See Office Action at page 1 Disposition of claims and at page 2, Status of Claims. Now claims 3, 4, 6, 8-12, 14, 30-35, 37-52, 54, and 56-60 are pending. Claim 3, 8, 39, 49-52, 54, and 57-60 are independent.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 56 has been rejected under 35 U.S.C. § 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically the Examiner objects to the following portion of the claim: "the particle has the same pharmacological activity and physico-chemical properties, chemical purity and physical form as the particles before sterilization." The Examiner asserts "these properties are not defined in either claim [56 or 51 from which 56 depends], thereby rendering the claim vague and indefinite." See Office Action at page 2. Applicants have amended claim 56 to remove pharmacological activity and physico-chemical properties from the claim. Applicants respectfully submit that chemical purity and physical form are specific defined properties of the product and as such are not vague or indefinite. Finally a chemical that is purified by irradiation sterilization and undergoes the resulting chemical degradation does not "have the same chemical purity and physical form as the particles before sterilization" as indicated in claim 56.

For at least these reasons claim 56 is not indefinite. Applicant's respectfully request reconsideration and withdrawal of this rejection

Rejections under 35 U.S.C. § 103

Claims 3, 4, 6, 34, 35, 39, 41, 45-47, 49-52 have been rejected under 35 U.S.C § 103(a) as being unpatentable over WO 96/32095 to Jakupovic et al. ("Jakupovic") combined with Bussey et al. ("Bussey"). See pages 3 and 4 of the Office Action. Claim 3 is independent with claims 4, 6, 34, 35, and 47 depending therefrom. Claim 39 is independent with claims 41, 45, 46 depending therefrom. Claims 49-52 are each independent.

Independent claims 3, 39, and 52 and the claims that depend therefrom

Applicants have discovered a pharmaceutically acceptable powder in the form of dry, finely divided heat sterilized particles in which the powder is essentially free of unknown foreign steroids formed from the degradation of the glucocorticosteroid. See claims 3, 39 and 52.

For the sake of expediting prosecution, claims 3, 39 and 52 have been amended to include in which the powder is essentially free of unknown foreign steroids formed from the degradation of the glucocorticosteroid. Neither Jakupovic nor Bussey alone or in combination teaches a powder in which the powder is essentially free of unknown foreign steroids formed from the degradation of the glucocorticosteroid. Jakupovic does not discuss sterilization and does not discuss degradation at all, while Bussey specifically identifies a degradation rate associated with its sterilization method. See Bussey at page 53. The combination of Jakupovic and Bussey do not teach or suggest a pharmaceutically acceptable powder in the form of dry, finely divided heat sterilized particles in which the powder is essentially free of unknown foreign steroids formed from the degradation of the glucocorticosteroid. A compound that is 99% pure using heat sterilization is distinguishable from one that is 99% pure after irradiation sterilization because the irradiation sterilization product will have unknown foreign steroids formed from the degraded glucocorticosteroids.

For at least these reasons claims 3, 39 and 52 and the claims dependent therefrom are patentable over Jakupovic and Bussey. Applicants respectfully request reconsideration and withdrawal of this rejection

Independent claims 49-51 and the claims that depend therefrom

Applicants have discovered a pharmaceutically acceptable powder and a sterile pharmaceutical formulation in the form of heat sterilized, dry, finely divided particles comprising budesonide, rofleponide or rofleponide palmitate, or ester, acetal, or salt thereof. See independent claims 49, 50, and 51.

The combination of Jacupovic and Bussey fails to disclose heat sterilized, dry, finely divided particles comprising budesonide, rofleponide or rofleponide palmitate, or ester, acetal, or salt thereof. Jacupovic discloses preparation of budesonide powder from a solution of budesonide in methanol. Jacupovic does not teach or suggest heat sterilized, dry, finely divided particles comprising budesonide, rofleponide or rofleponide palmitate. Bussey shows irradiation sterilization of 4 steroids hydrocortisone acetate, isoflupredone, methylprednisolone acetate, and prednisolone hydrous. Bussey does not teach or suggest heat sterilized dry, finely divided particles comprising budesonide, rofleponide, or rofleponide acetate. The combination of Jacupovic and Bussey does not teach or suggest heat sterilized finely divided particles comprising budesonide, rofleponide or rofleponide acetate.

The Examiner asserts that Jacupovic discloses respirable particles, and that Bussey teaches the desirability of sterile pharmaceutical products and thus there is motivation to combine the teachings. See Office Action at page 3. Applicants respectfully disagree. Bussey teaches a method of sterilizing 4 steroids: hydrocortisone acetate, isoflupredone, methylprednisolone acetate, and prednisolone hydrous using irradiation and mentions that EO irradiation exists but has certain problems. Bussey does not teach anything about the desirability of sterile pharmaceutical products. Bussey does not indicate any advantage or disadvantage of sterile steroids, does not indicate that sterilizing steroids is a desirable process, and does not speak generally to pharmaceutical products at all.

In a past office action, the Examiner asserts that one of skill in the art would have been motivated to sterilize the respirable particles to prevent microbial growth in the packaged material with a reasonable expectation of success. See Office Action of March 25, 2003. Applicants disagree. To begin with the FDA does not require that inhalation powders be sterile.

See draft Guidance for Industry: Metered Dose Inhaler and Dry Powder Inhaler Drug Products (a copy of which is provided at Tab A. Specifically the FDA asks for USP 61 microbial limits testing- which is for nonsterile products. See lines 239-240). So one truly of skill in the art would not be motivated to sterilize an inhalation powder at additional expense for the mere reason that it is a pharmaceutical. Secondly, the Guidance discusses the need to identify all recurring impurities that are greater than 0.1% of the final product. See Guidance at lines 246-257. Thus, one of skill in the art would wish to minimize these impurities by minimizing the process steps that might add to the number and amount of impurities, such as the degradation products associated with irradiation sterilization, and residues associated with EO sterilization as taught by Bussey. As a result, the artisan would not be motivated to use the method of Bussey to sterilize an inhalation powder. In fact, an artisan making an inhalation powder would not be motivated to combine the teachings of Bussey with the teachings of Jacupovic.

For at least these reasons claims 49-51 and the claims dependent therefrom are patentable over Jacupovic in view of Bussey. Applicants respectfully request reconsideration and withdrawal of this rejection.

Dependent Claim 56

Claim 56 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jacupovic in view of Bussey. See Office Action at page 5.

Applicants have discovered a pharmaceutically acceptable powder in the form of heat sterilized, dry, finely divided particles, said powder being sterilized by heat treatment at a temperature of from 100°C to 130°C and comprising budesonide, rofleponide or rofleponide palmitate, or ester, acetal or salt thereof, wherein the particles have the same chemical purity and physical form as the particles before sterilization. See claim 56.

As previously discussed, there is no motivation to combine Jacupovic with Bussey. In addition, the Examiner asserts that a compound that is irradiation sterilized and the resulting product is 99% pure (despite the admitted chemical degradation associated with irradiation sterilization) is indistinguishable from one that is heat sterilized and is also 99% pure. Respectfully, given the plain language of claim 56, the Examiner is making the wrong

comparision. Claim 56 clearly states that the particles have the same chemical purity and physical form before and after sterilization. Thus, the chemical purity and physical form that should be compared is not irradiation sterilized versus heat sterilized, but rather the before irradiation sterilization with the after irradiation sterilization and the before heat sterilization with the after heat sterilization. The result of the chemical degradation associated with irradiation sterilization is that the chemical purity and physical form have been changed by the degradation.

For at least these reasons claim 56 is patentable over Jacupovic in view of Bussey.

Applicants respectfully request reconsideration and withdrawal of this rejection.

Jacupovic in view of Bussey and Sequiera

Claims 8-12, 14, 30, 31, 43, 44, 48 and 54 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jacupovic, in view of Bussey, further in view of U.S. Patent No. 5,837,699 to Sequiera *et al.* ("Sequiera"). See Office Action at page 5. Claims 8-12, 14, 43, 44 and 48 depend from independent claim 8, claims 30, 31 depend from independent claim 3, and claim 54 is independent.

Independent claims 3 and 8 and the claims that depend therefrom

Amended claims 3 and 8 are patentable over Jacupovic in view of Bussey and further in view of Sequiera for at least the reason that none of Jacupovic, Bussey or Sequiera alone or in combination teach or suggest an inhalation powder in which the powder is essentially free of unknown foreign steroids formed from the degradation of the glucocorticosteroid. Jacupovic and Bussey have previously been discussed. Sequiera fails to cure the deficiencies of Jacupovic and Bussey. Specifically, Sequiera does not provide a sterile inhalation powder in which the powder is essentially free of unknown foreign steroids formed from the degradation of the glucocorticosteroid. Furthermore, as previously discussed, there is no motivation to combine Jacupovic with Bussey, and for similar reasons, no motivation to combine Sequiera with Jacupovic and Bussey.

For at least these reasons claims 3 and 8 and the claims that depend therefrom are patentable over Jacupovic in view of Bussey and further in view of Sequiera. Applicants respectfully request reconsideration and withdrawal of this rejection.

Independent claim 54

Applicants have discovered a pharmaceutically acceptable suspension comprising heat sterilized, finely divided particles comprising budesonide, rofleponide or rofleponide palmitate, or ester, acetal or salt thereof, combined with a pharmaceutically acceptable additive. See independent claim 54.

None of Jacupovic, Bussey, or Sequiera, alone or in combination teach or suggest a pharmaceutically acceptable suspension comprising heat sterilized, finely divided particles comprising budesonide, rofleponide or rofleponide palmitate, or ester, acetal or salt thereof, combined with a pharmaceutically acceptable additive. Furthermore, as discussed previously, there is no motivation to combine the teachings of Jacupovic with Bussey, and for similar reasons there is no motivation to combine Sequiera with Bussey.

For at least these reasons, claim 54 is patentable over Jacupovic in view of Bussey and further in view of Sequiera. Applicants respectfully request reconsideration and withdrawal of this rejection.

Jacupovic in view of Bussey and Radhakrishnan

Claims 32, 33 and 40 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Jacupovic in view of Bussey and further in view of U.S. Patent No. 5,192,528 to Radhakrishnan *et al.* ("Radhakrishnan"). Claims 32, 33 depend from independent claim 3 and claim 40 depends from independent claim 39.

Independent amended claims 3 and 39 are patentable over Jacupovic in view of Bussey and further in view of Radhakrishnan for at least the reason that none of Jacupovic, Bussey or Radhakrishnan alone or in combination teach or suggest an inhalation powder in which the powder is essentially free of unknown foreign steroids formed from the degradation of the glucocorticosteroid. Jacupovic and Bussey have previously been discussed. Radhakrishnan fails to cure the deficiencies of Jacupovic and Bussey. Radhakrishnan teaches an aqueous liposomal suspension, not an inhalation powder in which the powder is essentially free of unknown foreign steroids formed from the degradation of the glucocorticosteroid. Furthermore, as previously

discussed there is no motivation to combine Jacupovic with Bussey, and for similar reasons, no motivation to Radhakrishnan with Jacupovic and Bussey.

For at least these reasons, independent claims 3 and 39, and claims 32, 33 and 40 that depend therefrom are patentable over Jacupovic in view of Bussey and Radhakrishnan. Applicants respectfully request reconsideration and withdrawal of this rejection.

Jacupovic in view of Bussey, Sequiera and Radhakrishnan

Claims 8, 11, and 37 have been rejected under 35 U.S.C § 103(a) as being unpatentable over Jacupovic in view of Bussey, Sequiera and Radhakrishnan. Claim 8 is independent and claims 11 and 37 depend therefrom.

Independent amended claim 8 is patentable over Jacupovic in view of Bussey and further in view of Sequiera and Radhakrishnan for at least the reason that none of Jacupovic, Bussey, Sequiera or Radhakrishnan alone or in combination teach or suggest an inhalation powder in which the powder is essentially free of unknown foreign steroids formed from the degradation of the glucocorticosteroid. Each of these references has previously been discussed. The combination of them still fails to cure the deficiencies of the references individually. Furthermore, as previously discussed there is no proper motivation to combine the references as suggested by the Examiner.

For at least these reasons independent claim 8 and claims 11 and 37 that depend therefrom are patentable over Jacupovic in view of Bussey and further in view of Sequiera and Radhakrishnan. Applicants respectfully request reconsideration and withdrawal of this rejection.

New Claims 57-60

New claims 57-60 are believed to be patentable because they include a powder in which the powder contains not more than 0.38 % known and unknown foreign steroids formed from the degradation of the glucocorticosteroid. None of the cited references disclose, teach or suggest such a composition.

For at least these reasons claims 57-60 are patentable over the cited references.

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Conclusion

Applicant respectfully requests that all claims be allowed. Enclosed is a \$452 check for excess claim fees. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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